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Prevalence of abnormal pulmonary functions in Parkinson's disease and its correlation to the disease severity and quality of life

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ABSTRACT

Purpose: To know the effects of Parkinson's disease (PD) on pulmonary function parameters and the extent of this on the severity of the disease and quality of life to give more understanding of the nature of the disease and its effects. *Methods*: The study conducted at the neurology and chest departments of Mansoura university hospital, Egypt. The PD patients were subjected to pulmonary function tests, measurements for the strength of the respiratory muscles with their correlation with scales for quality of life (QOL) in PD and motor function. PD divided into 2 groups' normal pulmonary function (NPF) and abnormal pulmonary function (APF). *Results*: Fifty-two participants and the most common causes for APF (n =16) were restrictive (43.75%) and obstructive (25%). The APF patients showed a lower FEV1/FVC, FEV1and MEF50 and a high correlation with UPDRS total, modified H&Y, and S&E ADL. FEV1, FVC, PEF, and FEF25-75% showed a significant inverse correlation with bradykinesia. There was a significant inverse correlation between rigidity and these specific parameters FVC and PEF. MEP, FEF25-75%, and PEF associated with significant inverse correlations and UPDRS-III scores. Mobility domain scores correlated inversely with certain pulmonary functions MEP, FVC, PEF, and FEV1. *Conclusion*: There is an impairment of certain pulmonary function tests and respiratory muscles power in PD patients. Rigidity and bradykinesia showed the strongest association with the deterioration of those variables. All these abnormalities alter the quality of the daily activities of PD patients.

Keywords: Pulmonary function tests; Parkinson's disease; respiratory dysfunction; quality of life.

1. INTRODUCTION

Respiratory abnormalities play a curial role in neurodegenerative diseases (Troussière *et al.*, 2014). The presence of ventilatory dysfunction in Parkinson's disease (PD) was well known for many years, with underestimation of its prevalence. PARKINSON stated that a man who "fetched his breath rather hard" during his 1st description of the PD patient (Hovestadt *et al.*, 1989). Regarding the main causes of mortality in PD patients, pulmonary embolism and aspiration pneumonia are well known (Ebihara *et al.*, 2003), and ventilatory abnormalities are accountable for the morbidity accompanied by PD (Mehanna and Jankovic, 2010). Although pulmonary disorders were associated mostly with the impairment in the peripheral motor system (Baille *et al.*, 2016), many causes have been noted, including changes in central respiratory control, as well as obstructive and restrictive types. Ventilatory changes in patients with PD influence the patient's quality of life by decreasing physical activity levels (Mehanna and Jankovic, 2010). Pulmonary abnormalities in PD patients are due to a combination of many factors including central ventilatory control (direct brain stem involvement and substantia nigra-periaqueductal grey-retrotrapezoid nucleus pathway affection), drug--related side-effects (pulmonary fibrosis, dyskinesias, and neuroleptic-like malignant syndrome), restrictive changes (dysautonomia, myopathy, and rigidity/bradykinesia), and obstructive disease (direct basal ganglia involvement, and axial dystonia) (Torsney and Forsyth, 2017; D'Arrigo *et al.*, 2020).

The pathophysiology of PD showed degeneration of the substantia nigra pars compacta in the midbrain that associated with neurodegeneration in extranigral sites, particularly the brainstem nuclei related to sleep pathophysiology and respiration system control (Diederich and McIntyre, 2012; Braak *et al.*, 2003). So, the incidence of ventilatory dysfunctions in patients with PD is related to the degeneration of these specific parts of the brainstem. This study aims to know the effects of PD on pulmonary function parameters and the extent of this on the severity of the disease and quality of life to give more understanding of the pathophysiology of the disease and its effects.

2. PATIENTS AND METHODS

Research model and Participants

A single-centre, prospective cohort study was conducted on patients with idiopathic PD who were enrolled at the neurology department outpatient clinics of Mansoura university hospital, Mansoura, Egypt, during the period from August 2018 to the end of December 2020. All the PD participants were diagnosed as having idiopathic PD based on the PD published criteria (Gelb et al., 1999). The criteria for inclusion were as follows: patients diagnosed as PD; and without cognitive decline, as evaluated by the Mini--Mental State Examination (MMSE) (Norris et al., 2016). The criteria for exclusion were as follows: age below 40 years or above 80 years, history of pulmonary disease, previous history of thoracic surgery, any anatomical structural disorders of the chest cage, smokers, history of psychiatric diseases, psychotropic drugs usage, neurologic diseases other than PD, undergone neurosurgery to manage PD symptoms, failing to finish all of the required tests.

Ethical approval

Consent to share and ethics for all tests and examinations done in this study were in agreement with the ethical protocols of the institutional research committee and with the 1964 Helsinki Statement and its later modifications with ethical approval number R.21.07.1372.

Ventilatory function assessment

We studied the ventilatory functions including lung volume, spirometry, and pulse oximetry testing. These studies were done under the guidelines of the American Thoracic Society/European Respiratory Society (Wanger *et al.*, 2005). Maximal expiratory flow after expiration of 50% of FVC (MEF50), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV 1), peak expiratory flow (PEF), forced expiratory flow at 25 and 75% of the pulmonary volume (FEF25-75%), and oxygen saturation (SpO2) values were evaluated using a spirometer (Smart PFT Lab, Medical Equipment Europe GmbH, Germany) according to the standardized protocol (Miller *et al.*, 2005). All data of the ventilatory function tests were shown as ratios of the typical values predicted. PD participants diagnosed as having restrictive pattern with FVC < 80% and FEV1/FVC > 80%, peripheral obstructive pattern with MEF50 < 70%, and central obstructive pattern with FEV1 < 80% and FEV1/FVC < 80% (Sabaté *et al.*, 1996). Maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP) were measured by a digital manometer for the respiratory muscle strength (Micro MPM; Micro Medical, UK) according to the standardized protocol (Klefbeck et al., 2003). The PD participants were classified by dividing them into two groups based on their ventilatory function test results: abnormal pulmonary function (APF) group and normal pulmonary function (NPF).

Disease severity and the quality of life in PD

We used the following tests the standardised scale for assessing Parkinson's disease "unified Parkinson disease rating scale" (UPDRS) ('The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations.', 2003), modified Hoehn and Yahr staging (H & Y) scale (Goetz *et al.*, 2004), Schwab and England (S & E) activities of daily living (ADL) scale during the "OFF" state (Shulman *et al.*, 2016), and 39-item Parkinson's disease questionnaire (PDQ-39) to assess functional status and the disease severity of each PD participant (Jenkinson *et al.*, 1997).

Assessment of the severity of PD

First, we used subscale III of the UPDRS (UPDRSIII) to assess the motor function during PD participants in an "on" state of levodopa usage (Palmer *et al.*, 2010). The UPDRS evaluate the clinical picture of PD and specific activities by self-reporting. It includes 42 items classified into four components: I) mentation, mood and behaviour; II) activities of daily living; III) motor examination; and IV) complications of therapy. Each component ranges from normality (0) to disabling disease (4). The UPDRS-III evaluated by a health care professional (The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations, 2003). Second, the H & Y scale assess the progression of PD. It includes 5 stages and it was originally described in 1967. It is modified with the addition of stages 1.5 and 2.5 to express the intermediate progression of the course of PD (Goetz *et al.*, 2004).

Assessment of the quality of life in PD

First, we used the 39-item Parkinson's disease questionnaire (PDQ-39) to assess the quality of life (Jenkinson *et al.*, 1997). The PDQ-39 is classified into eight sections, with scores range from 0 to 100 on a scale of one to one hundred. A lower score expresses a better quality of life. We made a correlation between ventilatory function tests and the power of the respiratory muscles and the total score and mobility section score. Second, the S & E assess ADL scale during levodopa usage "OFF" state. It measures the quality of the daily activities of PD participants (Shulman *et al.*, 2016).

Statistical analysis

We used SPSS software, version 22, for Windows (SPSS, Chicago, IL) for all statistical analyses. The Pearson chi-squared test and the 2-sample Student t-test were used to evaluating the group comparison of age and sex. The covariates differences of age, sex, clinical severity, and pulmonary function parameters were assessed by analysis of covariance (ANCOVA). The mean ± standard deviation (SD) was used for all data. The P-value for relevance in statistics was set at < 0.05. The correlation between the quality of life, functional variables, and symptoms of PD were evaluated by Pearson's correlation coefficient.

3. RESULTS

Table 1 and figure 1 showed the recruited 52 PD participants (16 APF patients and 36 NPF). The APF group was 10 males and 6 females with a mean age of 65.32 ± 9.4 years, while the NPF group (control group) was 20 males and 16 females with a mean age of 61.43 ± 10.5 years. Both groups had ages and sex distributions that are similar. Table 2 showed the frequency of different causes in PD with APF. The first cause is a restrictive defect (43.75 %) followed by an obstructive defect (25%) then pneumonia and central ventilatory dysfunction 12.5 % and lastly drug-induced (6.25 %).

Table 1 Demographic and pulmonary functions of PD participants in NPF Group and APF Group

Number (%) Mean ± SD	APF group 16 (30.7%)	NPF group 36 (69.3%)	P-value
Age (Y)	65.32 ± 9.4	61.43 ± 10.5	0.34
Sex (M/F)	10/6	20/16	0.64
Pulmonary function parameters			
FVC (% pred)	79.5 ± 17.9	90.4 ± 9.1	0.02
FEV1 (% pred)	81.3 ± 16.3	91.2 ± 8.2	< 0.005*
FEV1/FVC	79.7 ± 9.0	86.8 ± 4.8	< 0.005*
MEF 50 (%)	73.9 ± 19.8	89.9 ± 9.1	< 0.005*
SpO2 (%)	93.6 ± 4.2	95.1 ± 2.6	0.65

M: male, F: female, APF: Abnormal Pulmonary Function, NPF: Normal pulmonary function, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, MEF50: Maximal Expiratory Flow after expiration of 50% of FVC, SpO_2: oxygen saturation. All data are presented as mean ± standard deviation, *P < 0.05

Table 2 Causes and types of respiratory dysfunctions in Parkinson's disease

Respiratory dysfunctions	Number of patients (%)
Restrictive defect	7 (43.75 %)
Obstructive defect	4 (25%)
Pneumonia	2 (12.5 %)
Central ventilatory dysfunction	2 (12.5 %)
Drug-induced	1 (6.25 %)

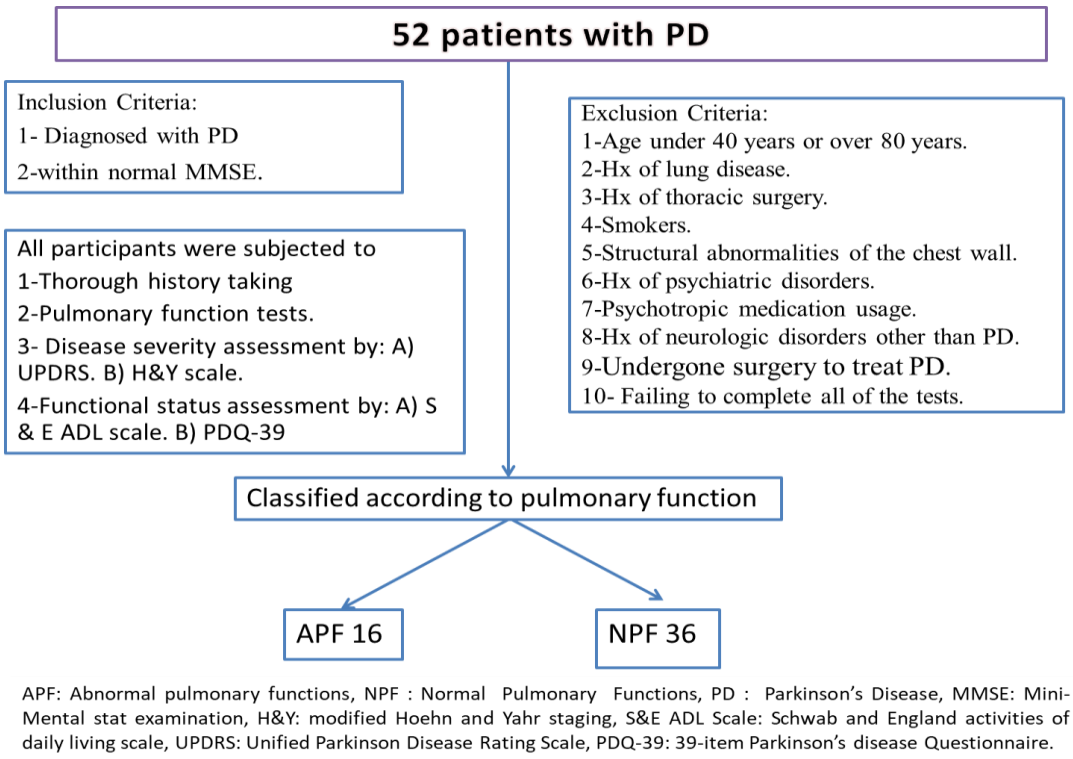


Figure 1 Study flow chart of the participants

The APF group showed a statistically significant lower FEV1, MEF50, and FEV1/FVC values than the NPF group. The APF group showed a high statistically significant correlation with UPDRS total, Modified H & Y, and S & E ADL. That means PD patients with APF were with more severe PD manifestations and worse quality of life (table 3).

Table 3 Relationship of pulmonary function test results and the severity of PD

Number (%) Mean ± SD	APF group 16 (30.7%)	NPF group 36 (69.3%)	P-value
UPDRS I N	4 (25%)	19 (52.7%)	P = 0.04
UPDRS II N	5 (31.3%)	12 (33.3%)	
UPDRS III	7 (43.7%)	5 (14%)	
UPDRS total	44.5 ± 29.8	37.4 ± 21.1	P < 0.005*
Modified H & Y	2.3 ± 1.2	1.7 ± 1.1	P = 0.01*
S & E ADL	80.4 ± 11.9	85.6 ± 12.3	P = 0.01*

APF: Abnormal Pulmonary Function, Modified H & Y: Modified Hoehn and Yahr staging scale, NPF: Normal Pulmonary Function, PD: Parkinson's disease, S & E ADL: Schwab and England Activities of Daily Living Scale, UPDRS: Unified Parkinson Disease Rating Scale

Specific pulmonary function variables were significantly related to rigidity and bradykinesia. Rigidity correlated inversely with FVC and PEF. Bradykinesia correlated inversely with PEF, FEV1, FVC, and FEF25-75%. Regarding the motor function, UPDRS-III scores correlated inversely withPEF, FEF25-75%, and MEP (table 4).

Table 4 Ventilatory muscle power and pulmonary function parameters and their correlation with PD cardinal signs and the total Unified PD Rating Scale subscale (motor examination) scores.

Variable	Cardinal signs			Motor function
	Rest tremor	Rigidity	Bradykinesia	Total UPDRS
FVC				
r	0.16	−0.40 *	−0.46 *	−0.31
p	0.28	< 0.05	< 0.05	0.10
FEV1				
r	0.23	−0.33	−0.41*	−0.32
p	0.20	0.09	< 0.05	0.09
FEV1/FVC				
r	0.26	0.24	−0.10	-0.11
p	0.18	0.19	0.43	0.41
PEF				
r	−0.14	−0.46 *	−0.48 *	−0.42 *
p	0.32	< 0.05	< 0.05	< 0.05
FEF25-75%				
r	0.19	−0.34	−0.50 *	−0.43 *
p	0.24	0.09	< 0.05	< 0.05
MIP				
r	−0.15	0.18	0.26	0.26
p	0.32	0.26	0.18	0.18
MEP				
r	−0.14	−0.29	0.34	−0.43 *
p	0.32	0.12	0.08	< 0.05

PEF: Peak Expiratory Flow, MIP: Maximum Inspiratory Pressure, FEF25-75%: Forced Expiratory Flow at 25 and 75% of the pulmonary volume, FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in 1 s, UPDRS: Unified Parkinson's Disease Rating Scale. MIP: Maximal inspiratory pressure, MEP: Maximum Expiratory Pressure, *Pearson's correlation; $p < 0.05$.

The frequency of clinical parameters affected in the APF group is as follow bradykinesia then UPDRS-III then rigidity. The PDQ-39 mobility domain scores and the total PDQ-39 scores were correlated inversely with PEF, FVC, FEV1, and MEP (table 5). That means the APF group are more suffering from a worse quality of life. Spirometry results of a patient diagnosed as PD showed abnormal pulmonary functions of restrictive pattern with small airway obstruction (figure 2).

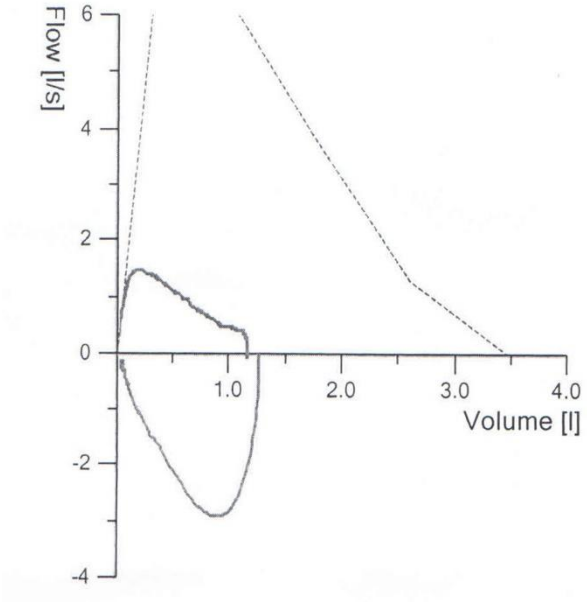
Table 5 Ventilatory muscle power and pulmonary function parameters and their correlation with quality-of-life questionnaire scores in patients with Parkinson's disease

Variable	Quality of life	
	PDQ-39	PDQ-39 mobility domain
FVC		
r	−0.50 *	−0.49 *
p	< 0.05	< 0.05
FEV1		
r	−0.48 *	−0.47 *
p	< 0.05	< 0.05

FEV1/FVC		
r	0.31	0.28
p	0.10	0.12
PEF		
r	−0.42 *	−0.41 *
p	< 0.05	< 0.05
FEF25-75%		
r	−0.30	−0.32
p	0.11	0.09
MIP		
r	0.31	0.33
p	0.10	0.09
MEP		
r	−0.53 *	−0.48 *
p	< 0.05	< 0.05

PEF: Peak Expiratory Flow, MIP: Maximum Inspiratory Pressure, FEF25-75%: Forced Expiratory Flow at 25 and 75% of the pulmonary volume, FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in 1 s, UPDRS: Unified Parkinson's Disease Rating Scale, MIP: Maximal inspiratory pressure, MEP: Maximum Expiratory Pressure, PDQ-39: 39-Parkinson's Disease Questionnaire, *Pearson's correlation; $p < 0.05$.

(A)



(B)

	Unit		Pred.	Pre	%Pred.
VC	l	(1)	3.60		
VC	l	(1)	3.60	1.27	35%
FEV1	l	(1)	2.72	0.96	35%
FEV1/FVC	%	(1)	76	82	109%
FEV1/VC	%	(1)	76	75	100%
PEF	l/s	(1)	7.49	1.47	20%
MEF75	l/s	(1)	6.65	1.38	21%
MEF50	l/s	(1)	3.89	0.97	25%
MEF25	l/s	(1)	1.28	0.57	45%

Figure 2 Spirometry results for a PD patient with abnormal pulmonary functions, A) flow volume loops, and B) data table.

4. DISCUSSION

PD patients had many manifestations of motor and nonmotor (Chahine et al., 2017). Many PD patients do not complain of pulmonary function abnormalities, this gap had been attributed to the fact that as the PD disease progress the pulmonary function abnormalities may pass unnoticed. As the disease progresses, due to the physical disability this will lead to an inactive life, which decreases the physical efforts leading to flaring up the manifestations of pulmonary dysfunctions (Sathyaprabha *et al.*, 2005). Therefore, chest exercises become crucial when the PD patient becomes inactive, and physical activity and muscular exercises are important as respiratory rehabilitation programs (Köseoğlu *et al.*, 1997). The weakness in the respiratory muscle that occurs in PD

patients could be as a result of the progressive decrease of the chest wall movement leading to a decrease in the reduced tidal volume (Frazão *et al.*, 2014).

Consequently, the reduced muscle adaptability and regulation from thoracic spine rigidity, postural changes from the increased kyphosis, and rib cage inflexibility as a result of PD manifestations will lead to decrease MIP and MEP values (Cardoso and Pereira, 2002). Tremors, chest muscle stiffness, and bradykinesia could affect lung ventilation in PD patients (Cardoso and Pereira, 2002; Guedes *et al.*, 2012). The defect in the physiology of the respiratory system as the result of parasympathetic hyperactivity can lead to constriction of the airway smooth muscle (Mikaelee et al., 2006). This study aims to evaluate the impacts of PD on respiratory functions and the consequences on the quality of daily activities and the severity of the disease. To achieve this aim we enrolled 52 PD participants and divided them into 2 groups APF and NPF. The selection of PD with NPF as a control group was to achieve a more accurate comparison. The study design tried to be more precise with certain inclusion and exclusion criteria. Part of the study was done during the pandemic of COVID-19 and it was a great challenge to work under safety measures and to protect the patients and the health care providers; this one of the causes that lengthens our study duration.

Our results are following Sathyaprabha *et al.*, (2005) who stated that "Individuals with PD have significantly decreased respiratory muscle strength than those without the condition". Seccombe *et al.*, (2011) stated that "In 68% and 79% of patients, MIP and MEP were below the normal range, respectively". They found "Improvement in MIP and MEP in PD patients on levodopa compared to those who aren't". These findings are in line with previous research of Weiner *et al.*, (2002). In the present research, specific pulmonary functions (FEV1, FEV1/ FVC, and MEF50) showed a significant decrease in the APF group. As this group showed the restrictive pulmonary disease, the most typical modifications being reduced minute volume, reduced tidal volume, and reduced inspiratory flow. These respiratory dysfunctions were correlated with cardinal signs of PD respiratory muscle stiffness and hypokinesia (Sathyaprabha *et al.*, 2005; Seccombe *et al.*, 2011). Many colleagues reported several changes in the respiratory mechanics and lung ventilation in the APF group. While respiratory manifestations are uncommon in the early phases of PD (Sathyaprabha *et al.*, 2005; De Pandis *et al.*, 2002). Potential interpretations for the decreased lung capacity and volume are as follow diaphragmatic flutter (Weiner *et al.*, 2002); reduced upper airway muscle function influencing airflow resistance and leading to flow flutter (Vincken et al., 1986); and decreased MEP (Wang *et al.*, 2014). Motor function and UPDRS-III scores were correlated inversely with the following pulmonary function tests: FEF25-75%, PEF, and MEP. A decline in motor function (i.e., a higher UPDRS-III score) translates to lower specific pulmonary function.

The mechanics of the respiratory system in PD patients are affected by abnormal motor function and the decreased thoracic movements that lead to osteoarticular degeneration and postural misalignment (Owolabi et al., 2016). Both rigidity and bradykinesia especially during off periods lead to more motor manifestations lead to reduced respiratory system mechanics and impaired pulmonary function (Estenne et al., 1984; Yust-Katz *et al.*, 2012). The results of this study are in agreement with another study findings in which an inverse correlation was observed between PDQ-39 scores and PEF in patients with PD (Yust-Katz *et al.*, 2012). The total PDQ-39 scores, quality of life, and scores on the mobility domain of the PDQ-39 demonstrated an inverted association with FVC, FEV1, MEP, and PEF. As the PD disease develops, motor function alterations adversely influence the mental, physical, socioeconomic, and emotional condition leading to poor quality of life. Similarly, reduced mobility resulting in decreased ADL, social isolation with advanced impairment of respiratory functions with more pulmonology complications (Lim *et al.*, 2008).

The explanation of the existence of pulmonary dysfunction in PD could be explained by dysfunction in the brainstem centres and basal ganglia which control the peripheral airway muscles and the central respiratory drive. So, it is logical to suppose the existence of some kind of dysfunction in other forms of Parkinsonism (Jankovic and Tintner, 2001). Despite the importance of the identification of the consequences of the pulmonology functions changes and ventilatory mechanics on the quality of the daily activities of PD patients, few researchers have evaluated this idea, more investigations and researches, thus, are needed.

Limitations of our study

The relatively small sample size precludes firm conclusions. The other issues that need to be covered like studying of apnoea in PD, the impacts of dopaminergic medications as protection or risk for respiratory function changes, the association between pulmonary medications and PD, deep brain stimulation in PD and respiratory failure, and the respiratory dysfunction in other Parkinsonisms like multiple system atrophy and dementia with Lewy bodies.

5. CONCLUSION

There is an impairment of certain pulmonary function tests and respiratory muscles power in PD patients. Rigidity and bradykinesia showed the strongest association with the deterioration of those variables. All these abnormalities alter the quality of the daily activities of PD patients. So, PD with APF showed more affection for motor activities and quality of life.

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Author Contributions

This work was carried out in collaboration among all authors.

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This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethical approval

The study was approved by the Medical Ethics Committee of Mansoura University (ethical approval code: R.21.07.1372).

Data and materials availability

All data associated with this study are present in the paper.

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